Huntington's Disease Society of America

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Presenter Disclosures

Samuel Frank, MD

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

Consultant to Lundbeck
Speaker for Allergan

Huntington's Disease Society of America

Progression of Huntington's Disease

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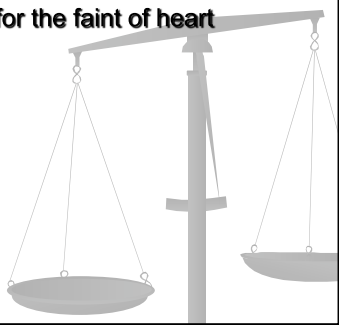
Additional Disclosure

- This talk is not for the faint of heart



Overview

- The starting point
- The finish line
- The many years between
  - Reasons for decline
  - Maintaining independence
  - Improving quality of life

Gene Test – CAG Repeats

- Accurate gene test for individuals has been available since 1993
- 98.9% sensitivity
- Median number of repeats is 44
  - Range from 36-121
- Number of repeats does not determine course or severity of disease, but does generally correlates with age at onset.

Early Disease Features

- Chorea
- Personality changes
- Behavioral problems
- Clumsiness
- Subtle walking changes
- Mild speech rate and rhythm problems
- Memory problems
- In retrospect, often have preceding mood disorder, decline at work, or relationship difficulties.

Advanced Disease

- Stiffness and slowness of movement
  - More prominent than chorea, but chorea can also re-emerge
- Dystonia (Abnormal fixed postures)
- Weight loss
- Dementia
- Rate of progression varies, but duration of disease ranges from 10-25+ years

Causes of Death

- Causes of death are typically related to loss of movement:
  - Pneumonia
  - Aspiration
  - Nutrition
  - Chronic skin ulcers
- Suicide
  - ~ 25% attempt at least once
  - 8-9% of all deaths due to completed suicide
  - Risk factors include childlessness, depression, single, living alone, other suicides in family

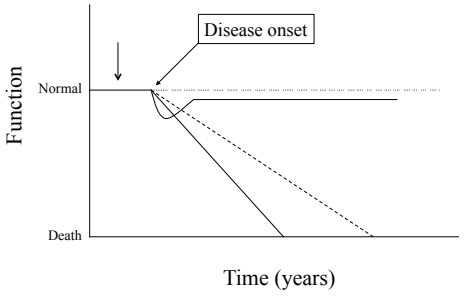
HD Staging

- Based on 13 point Total Functional Capacity (TFC) score
  - Occupation (3 points)
  - Finances (3 points)
  - Domestic Chores (2 points)
  - ADL (3 points)
  - Care Level (2 points)
- Stage 1 = 11-13, 2 = 7-10, 3 = 3-6, 4 = 1-2, 5 = 0
- Typically lose ~1/2 point per year
- Not good for children/young adults, those with prominent psychiatric disease, or late stages.

Measuring Function

- TFC
- Functional checklist
  - 25 items
  - Ability or inability to do tasks
- Independence scale
  - 0-100% of 'normal' function
  - 5-10% increments

Changing Disease Progression



Disease-Modifying Strategies

- None proven to slow disease
- CoEnzyme Q10 (CARE-HD)
  - 13% slowing of the staging scale decline
  - 2CARE underway
- Creatine
- Others
  - Minocycline, blueberry extract, trehalose, omega 3 fatty acids (fish oil, ethyl-EPA), antidepressants (SSRI's)

What Is Associated with Disability?

- Early HD
  - Not studied well or extensively
- Late HD
  - Motor and cognitive difficulties

What is Associated with Disability?

- Although one of the most asked questions by patients, not well studied.
- Studies to date conclude:
  - Cognitive dysfunction is an important determinant of disability
  - Motor effects tend to be more disabling later
  - Treating motor aspects of HD tends to have little impact, but needs further study
- However, most studies examine mid-stage disease and not pre-symptomatic or early disease

I Shoulson, 1981

- 10 men, 12 women studied
- Treatment of chorea and depression out of proportion to physical disability
- In the first 7 years of HD, occupation capacities and financial management skills were most affected
- Improvement in chorea and depression was temporary and did not change functional outcome

R Mayeux, 1986

- Followed 33 patients over 'several years'
- Intellectual impairment and depression correlated with reduced functional capacity.
  - When somatic symptoms eliminated, no longer significantly associated
- There was no association of functional disability with:
  - Duration of illness
  - Motor disability
  - Age at onset

A Feigin, 1995

- Followed 129 people
- As functional capacity worsened, chorea lessened and dystonia intensified.
- No correlation between rate of functional decline and:
  - age at onset of HD
  - body weight
  - gender of affected parent
  - history of neuroleptic use.

K Marder, 2000

- 960 patients were followed for 18 months
- TFC declined by 0.72 units/year, faster for those with score of 7-13 at baseline
- Associated with less rapid decline in TFC:
  - Longer disease duration
  - Better cognitive status at baseline
- Associated with more rapid decline in Independent Scale:
  - Depression symptoms
- No effect:
  - Age at onset of HD, sex, weight, or education

N Mahant, 2003

- 1,026 patients followed for median of 2.7 years
  - From HSG UHDRS database
- All stages of disease studied
- Conclusions:
  - Rate of progression was associated with younger age at onset
    - ?CAG repeat length implications
  - Chorea was associated with weight loss, but chorea and dystonia were not major determinants of disability
    - Based on scale totals

JM Hamilton, 2003

- 22 patients
- Apathy and executive dysfunction behavioral index was strongly related to decline in ADL's
- Behavioral dysfunction may impede ability to use motor or cognitive skills that remain available in early HD
- JC Rothlind et al, 1993 also examined higher level of control and dysfunction in early HD:
  - Psychomotor speed
  - The ability to regulate attention

V Wheelock, 2003

- Used 3,070 patients with clinically definite HD in HSG UHDRS database
  - 228 resided in nursing homes
- For 1,559 patients, there was longitudinal data for 1.9 years
  - 87 patients moved from home to nursing home

V Wheelock, 2003: Findings

- NH residents had worse motor function:
  - Chorea, bradykinesia, gait abnormality, and imbalance
- More likely to have behavioral disease:
  - Obsessions, compulsions, delusions, auditory hallucinations
  - More aggressive, disruptive and irritable behaviors

V Wheelock, 2003

- Predictive of NH placement:
  - Impaired gait
  - Impaired tandem walking
  - Bradykinesia
- Important conclusion: motor variables alone predicted NH placement

S Frank, TBA

- CARE-HD database
- 347 participants at baseline
- Association examined between chorea, other motor items and TFC and Functional Checklist (totals and individual items)
- Disabilities associated with chorea:
  - Employment
  - Driving
  - Caring for children
  - Doing housework

S Frank, TBA

- TFC total was also associated with severity of chorea
- Individual items from TFC associated with chorea:
  - Occupation
  - Domestic chores

What Is Needed?

- COHORT
- The "Framingham Heart Study" of HD
- Prospectively follow:
  - Symptomatic HD
  - Gene positive, pre-symptomatic
  - At risk
  - Controls

Treatments - Symptomatic

- Movement disorders
- Psychiatric treatments
- Non-pharmacologic interventions
- All medications must be reconsidered with advancing disease

Treatments - Movements

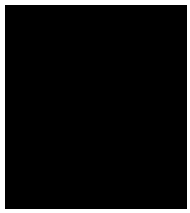
- Chorea
  - Medications
    - Must weigh benefit of reducing chorea vs. side effects
- Slowness and Stiffness
  - Anti-Parkinsonian drugs
- Dystonia
  - Botulinum toxin
  - Medications

Treatments - Psychiatric

- Depression
  - Antidepressants
- Hallucinations, abnormal beliefs
  - Neuroleptics
    - May have benefit on movements also
    - May cause weight gain
- Sleep
  - Behavioral measures
  - Hypnotics
  - Disruption of the house is one of the main determinants of nursing home placement in Alzheimer's disease

Treatment Strategies: Cognitive Disorder

- Memory
  - Recognition easier than recall
  - Provide hints, yes/no questions
- Learning
  - Provide simple & concrete instructions
  - Limit distractions
- Organization
  - Help pts with lists, calendar, and routines
- Bradyphrenia
  - Do not interpret a lack of response as a "NO" response
  - Have patience



Conclusions

- In early HD, occupation, finances and driving may be affected
- Attention and cognitive changes may impact functioning early in disease
- Motor features (specifically chorea) may impact function early in HD
- A better understanding of HD may help with future treatments

Thank you!